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In vitro modulation of endogenous rhythms by AC electric fields: Syncing with clinical brain stimulation

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Humans are exposed to an increasing prevalence of weak and strong AC electric fields, as part of daily life in the modern world. Further, electric fields are being deployed to modulate brain function for research and clinical applications. A single electric field pulse, applied via transcranial electrical or magnetic stimulation, can transiently excite or disrupt activity in neural circuits. In contrast, extended exposure to steady electric fields or pulse trains can result in long-term effects on neural activity including potentiation or depression. In addition, it has been demonstrated that brain stimulation with electric fields can improve cognitive performance in normal subjects (Marshall *et al.* 2006). The impact of electric fields on brain function has motivated the development of therapies to treat a wide range of psychiatric and neurological diseases using transcranial electrical or magnetic stimulation (Wassermann & Lisanby, 2001), as well as deep brain stimulation with implanted electrodes.

The mechanisms by which electric fields affect brain function have not been fully elaborated. A recent report in *The Journal of Physiology* by Deans *et al.* (2007) presents new data on the interaction of AC electric fields down to a cellular level as well as with neuronal population dynamics. The report reveals a frequency-specific ability of AC electric fields to rhythmically polarize pyramidal neurons of the CA3 region of the hippocampus and demonstrates the ability of AC fields to alter pharmacologically induced endogenous oscillations in the hippocampus. These data have important implications for understanding the effect of environmental AC fields and therapeutic stimulation on the activity of neuronal ensembles. A central finding of this study is that an AC electric field, applied *in vitro* to a brain slice set to oscillate in the gamma frequency range through bath application of kainate, shifts the ongoing oscillation to centre on the applied field frequency or a subharmonic of that frequency. This review of Deans *et al.* (2007) is intended to elucidate the connection between their work and other recent *in vitro* findings concerning electric fields in the brain with some recent clinical findings pertaining to cognitive function and electric fields.

Sensitivity of CA3 pyramidal neurons to AC electric fields

An understanding of the frequency dependence of the passive membrane properties of individual CA3 pyramidal neurons to polarization by an electric field was pertinent towards subsequent characterization of the effects of AC electric fields on ongoing oscillations. Coupling of the electric field to the cell's transmembrane potential decreased exponentially with increasing stimulation frequencies, consistent with the commonly modelled resistor-capacitor circuit across the membrane. Sharp intracellular recording techniques were employed to record changes in transmembrane potential induced by the oscillating electric field applied across the transverse hippocampal slice. The results were reinforced with optical measurements, in order to ensure accurate passive electrical property measurements of the unperturbed cell membrane. At frequencies below 10 Hz, the electric field did not differ in its efficacy to polarize the neuron, while 50 Hz neared the minimum efficacy for the range of frequencies tested (up to 100 Hz), resulting in approximately one-third the polarization efficacy compared to DC electric field polarization. This relationship of polarization by an electric field at differing frequencies provides important information for the design of brain stimulation protocols, necessary when determining electric field strength at varying frequencies. For example, the response threshold in many TMS experiments is determined by single-pulse titration, whereas subsequent stimulation, with intensity normalized to this threshold, is at a higher frequency which could alter the effective threshold. In addition, the polarization enduced at 50 Hz, Europe's power line frequency, and a similar effect at the United States' 60 Hz power-line frequency (see Deans' supplementary material), reveals the minimum electric field magnitude shown to have an effect is well below the magnitude of environmental fields caused by power-lines.

AC electric field modulation of kainate-induced gamma band oscillations

Upon deducing the efficacy of AC fields on polarization, the ability of these fields to modulate ongoing kainate-induced gamma band (∼30 Hz) oscillations was demonstrated. Deans *et al.* show a 50 Hz AC electric field reducing the power at the ongoing oscillation frequency of 30 Hz, while shifting and increasing the power maximum slightly below this frequency to 25 Hz. Negative extracellular spikes in the ongoing gamma oscillation were shown to occur every other cycle of the 50 Hz AC field minima. On the other hand, when the control oscillation had a peak power of < 25 Hz (beta band) the field-induced modulation centred on 17 Hz or every third cycle. This effect of entrainment of the ongoing oscillation at the closest dividend of the field frequency may prove to have important clinical applications. Clinical studies have used a matching slow wave frequency field to provide entrainment of slow waves, though other frequencies may also prove effective for both slow wave and other oscillation band entrainment. This finding may allow clinical application of multiple band modulation such as theta modulated gamma or sleep spindles (12-20 Hz) with slow-wave sleep (i.e. matching one frequency band while maintaining a dividend of another).

Deans *et al.* show maximal firing preceding peak soma depolarization by 5 ms. Concomitantly with this study, it has been shown that AC electric fields can constrain the firing of a single CA1 pyramidal cell to the rising edge of the

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depolarization, with the degree of coherence governed by the ratio of extracellular field oscillation to intracellular drive towards firing threshold (Radman *et al.* 2007). Likewise, firing on the rising edge of an applied Gaussian waveform electric field occurred in either the positive or negative polarity (Francis *et al.* 2003). Francis *et al.* applied AC fields in the form of a series of positive or negative Gaussian pulses allowing entrainment of an elevated potassium-induced oscillation. They showed a dose-dependent response at this lower frequency field and oscillation, as did Deans *et al.* Both research groups were unable to detect an effect below 0.3 mV mm^{-1} field strength.

This work is particularly timely given increasing interest in the role of endogenous electric fields as neuronal signals, and clinical demonstration of applied weak current modulating memory and behaviour (Marshall *et al.* 2006). Marshall *et al.* recently employed transcranial electrical stimulation to humans during slow wave sleep to improve performance in a word-recall task (declarative memory). It was presumed this effect was due to the electric field boosting slow wave oscillations which have previously been implicated in learning. This is an exciting finding, and Deans *et al.* have provided timely *in vitro* evidence for an underlying mechanism. In Marshall *et al.* the electric field frequency was selected to match the desired oscillation to be modulated—slow wave sleep (< 1 Hz). In other studies, sleep slow waves were shown to be triggered with < 1 Hz transcranial magnetic stimulation pulses, though these pulses were of suprathreshold magnitude, and possibly induced slow waves through a different mechanism. Deans *et al.* have now shown that at these frequencies there is no reduction in polarization efficacy by an electric field from the maximum possible for a neuron.

It is remarkable that a 0.5 mV mm^{-1} electric field at 50 Hz, resulting in a peak polarization of 25 μV intracellularly, which is a small fraction of the difference between rest and firing threshold, has the ability to entrain an oscillating network. Deans *et al.*'s *in vitro* work is clearly important for clinical brain stimulation research. Corroborating and extending this study should provide enhanced understanding of the role of endogenous fields, as well as leading to greater specificity of electrical and magnetic stimulation, with fewer side-effects. A key objective of future work should be the *in vitro* examination of the chronic effects of stimulation. Such research could reveal ways to optimize therapeutic efficacy, though the disconnected nature of *in vitro* slice networks may limit the applicability of these results to the intact brain.

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